IMPACT OF TREATMENTS ON RADIOGRAPHIC PROGRESSION OVER THE FIRST 10 YEARS OF DISEASE IN EARLY RHEUMATOID ARTHRITIS: RESULTS FROM THE ESPOIR COHORT

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Background: Long-term observational studies on the prediction of structural damage progression (SDP) in rheumatoid arthritis (RA) have mostly considered patients baseline characteristics and have rarely evaluated the specific impact of treatments in real world settings.

Objectives: To assess the impact of treatments exposure on the 10-year radiographic progression in early rheumatoid arthritis (RA).

Methods: The 310 patients of the ESPOIR cohort fulfilling ACR/EULAR 2010 criteria at baseline and having complete radiographic data at baseline and 10 years were considered in the present study. SDP was defined at 10 years as a significant increase of the Sharp/van der Heijde score, i.e., superior to the Smallest Detectable Change of 11.5 at 10 years. Three RA treatments were considered: glucocorticoids (GC), conventional synthetic and biologic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs and bDMARDs), which posologies were standardized by the mean of dose quotients (DoseQ). Drug exposure was modelled with Weighted Cumulative Exposure (WCE) variables, considering the intensity of drug exposure defined as a weighted function of past doses, and was incorporated into a logistic regression model that also included baseline clinical, biological and radiological characteristics. The predictive performance of this WCE model was compared to models considering on the one hand only baseline characteristics (BSL model) and on the other, baseline characteristics and binary treatments exposure - in other terms, “ever exposed, yes or no” (BIT model).

Results: Overall, SDP at 10 years occurred in 85 (27.4%) patients. GC exposure was significantly associated with SDP in univariate analysis only, and therefore was not included in the final WCE model. In the final WCE model, the joint exposure to 1 DoseQ of csDMARD and 1 DoseQ of bDMARD during the 10-year follow-up was associated with a significant protective effect on SDP compared to patients receiving no treatment: OR=0.04 (95% CI: 0.002-0.72). Early csDMARD initiation was associated with a significantly lower risk of SDP compared to later initiation (Table 1).

Table 1. odds ratios for the association of patterns of drug regimen with 10-year radiographic progression

<table>
<thead>
<tr>
<th>Exposure tested</th>
<th>Reference</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments intakes during the last 10 years</td>
<td>csDMARD &amp; bDMARD for last 10 years</td>
<td>No treatment for last 10 years</td>
</tr>
<tr>
<td>Testing the interest of an early initiation of csDMARDs (not combined with bDMARD)</td>
<td>csDMARD for last 10 years</td>
<td>csDMARD after year 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>csDMARD after year 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>csDMARD after year 1</td>
</tr>
<tr>
<td>Testing the interest of an early initiation of bDMARDs (in combination with csDMARD)</td>
<td>bDMARD after month 3</td>
<td>No treatment for last 10 years</td>
</tr>
<tr>
<td></td>
<td>bDMARD after month 6</td>
<td>0.06 (0.002-0.072)</td>
</tr>
<tr>
<td></td>
<td>bDMARD after year 1</td>
<td>0.04 (0.002-0.072)</td>
</tr>
<tr>
<td></td>
<td>bDMARD after year 2</td>
<td>0.04 (0.003-0.73)</td>
</tr>
<tr>
<td></td>
<td>bDMARD after year 3</td>
<td>0.05 (0.03-0.81)</td>
</tr>
</tbody>
</table>

Initiation of a bDMARD between the 3rd month and 3rd year of follow-up in combination with a csDMARD was significantly associated with a lower risk of SDP compared to no bDMARD treatment (Table 1). The final WCE model was better at predicting SDP at 10 years compared to the BSL and BIT models, with AUC=0.92 (95% CI: 0.89-0.95) (Figure 1).

Conclusion: CsDMARDs and bDMARDs have a protective effect on radiographic progression at 10 years in RA patients. This study has shown the value of considering drug exposure in the study of RA prognosis, and modeling this exposure using WCE variables.

Disclosure of Interests: Joanna KEDRA: None declared, David Hajage: None declared, Alexandre Lafourcade: None declared, Bernard Combe Grant/research support from: Novartis, Pfizer, Roche-Chugai, Consultant of: AbbVie; Gilead Sciences, Inc.; Janssen; Eli Lilly and Company; Pfizer; Roche-Chugai; Sanofi, Speakers bureau: Bristol-Myers Squibb; Gilead Sciences, Inc.; Eli Lilly and Company; Merck Sharp & Dohme; Pfizer; Roche-Chugai; UCB, Maxime Dougados Grant/research support from: AbbVie, Eli Lilly, Merck, Novartis, Pfizer and UCB Pharma, Consultant of: AbbVie, Eli Lilly, Merck, Novartis, Pfizer and UCB Pharma, Speakers bureau: AbbVie, Eli Lilly, Merck, Novartis and Pfizer and UCB Pharma, Bruno Fautrel Grant/research support from: AbbVie, Lilly, MSD, Pfizer, Consultant of: AbbVie, Biogen, BMS, Boehringer Ingelheim, Celgene, Lilly, Janssen, Medac MSD France, Nordic Pharma, Novartis, Pfizer, Roche, Sanofi Aventis, SOBI and UCB

DOI: 10.1136/annrheumdis-2020-eular.2635

DENDRITIC CELLS AS A PREDICTOR OF GOOD CLINICAL RESPONSE IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Dendritic cells (DCs) are known to contribute to the pathogenesis of rheumatoid arthritis (RA) through presentation of cartilage glycoprotein, production of proinflammatory cytokines and activation of Th1/Th17 responses. DCs are a heterogeneous population and can be divided into groups: myeloid (mDCs) and plasmacytoid (pDCs). DCs can induce both immune response and tolerance.

Objectives: To investigate the subpopulations of peripheral blood DCs (myeloid and plasmacytoid) in patients with early RA as a predictor of good clinical response to disease-modifying antirheumatic drugs (DMARDs) treatment.

Methods: Fifty two patients with early RA (duration of the disease up to 12 months) were included in the study. All patients fullfilled ACR/EULAR criteria (2010) and received methotrexate, lefluimone, sulfasalazine or their combination. Fifty five patients with osteoarthritis (OA) used as a control group. Analysis of the content of the B-lymphocytes, myeloid and plasmacytoid DCs was carried out by flow cytometry. B-lymphocytes, subtypes of peripheral blood DCs were characterized by the following phenotypes: myeloid DCs (CD3-CD14-CD19-HLA-DR+CD11c+CD123+) and plasmacytoid DCs (CD3-CD14-CD19-HLA-DR+CD11c+CD123+). B-lymphocytes (CD19+). Analyses were performed before treatment and after 3 and 6 months.

Results: Patients with early RA were characterized by significant evaluation of the population of myeloid DCs in comparison of patients with osteoarthritis (26.6% vs 23.5, p=0.0007). Furthermore, the difference was found in the number of cells with the phenotype B-lymphocytes: 5.4% vs 3%, p = 0.0005. No significant differences were observed in the number of plasmacytoid DCs. After 3 and 6 month of observation we detected reducing amount of myeloid DCs 26.6% vs 21.1% vs 18.4% respectively. Also we revealed reducing B-cells in treatment (5.4% vs 3 % vs 2%). Disease activity according to DAS28 dropped low (4.32 to 3.06, p=0.03). We also revealed a reliable negative correlation between both the activity of the disease and the B-cells (r=-0.4, p=0.05, n=52) and myeloid DCs (r=-0.6, p=0.0004, n=52). A reducing of the immune cells during the DMARDS therapy suggests that they are an attractive marker for good clinical response to the DMARDs.

Conclusion: The data obtained confirm the determining role of myeloid DC and B lymphocytes in maintaining systemic inflammation in rheumatoid arthritis. In addition, these cells are a target of DMARDs therapy and a predictor of a good clinical response.

Disclosure of Interests: None declared, Alexandre Lafourcade: None declared, Bernard Combe Grant/research support from: Novartis, Pfizer, Roche-Chugai, Consultant of: AbbVie; Gilead Sciences, Inc.; Janssen; Eli Lilly and Company; Pfizer; Roche-Chugai; Sanofi, Speakers bureau: Bristol-Myers Squibb; Gilead Sciences, Inc.; Eli Lilly and Company; Merck Sharp & Dohme; Pfizer; Roche-Chugai; UCB, Maxime Dougados Grant/research support from: AbbVie, Eli Lilly, Merck, Novartis, Pfizer and UCB Pharma, Consultant of: AbbVie, Eli Lilly, Merck, Novartis, Pfizer and UCB Pharma, Bruno Fautrel Grant/research support from: AbbVie, Lilly, MSD, Pfizer, Consultant of: AbbVie, Biogen, BMS, Boehringer Ingelheim, Celgene, Lilly, Janssen, Medac MSD France, Nordic Pharma, Novartis, Pfizer, Roche, Sanofi Aventis, SOBI and UCB

DOI: 10.1136/annrheumdis-2020-eular.2464

COMPARISON OF BONE SCINTIGRAPHY AND FDG-PET/CT IN THE EVALUATION OF DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS: VALIDATION OF BONE SCINTIGRAPHY

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Background: Clinical joint count assessment is important for detecting synovitis but its reliability is controversial

Objectives: This study assessed the correlation between bone scintigraphy and positron emission tomography (PET)-derived parameters in 28 joints with disease activity and compared the reliability of joint counts between bone scintigraphy and clinical assessment in rheumatoid arthritis (RA).

Methods: We enrolled 86 patients with active RA who underwent bone scintigraphy, fluorine-18-fluorodeoxyglucose (FDG) PET/CT and disease activity evaluation at the same time. This two-step study involved a development (n=67) and validation (n=19) group. Bone scintigraphy-derived joint assessment were compared with PET/CT derived and clinical joint assessment. Subsequently, we developed a disease activity score (DAS) using bone scintigraphy-positive joints and validated it in an independent group.

Results: The number of bone scintigraphy-positive joints in 28 joints was significantly correlated with the swollen (SJC) and tender (TJC) joint counts and PET/CT derived joint counts. Intra- and inter-observer reliabilities of bone scintigraphy for the affected joint counts were excellent. Inter-observer reliability between nuclear medicine physicians and rheumatologists was good for SJC/TJC and PET/CT derived joint counts in 28 joints except shoulders. After multivariate analyses including erythrocyte sediment rate (ESR) and patients global assessment (PGA) in addition to bone scintigraphy-derived parameters, bone scintigraphy/DAS was derived as 0.056 × number of bone scintigraphy-positive joints and DAS28-ESR was confirmed in the validation group (p<0.001).

Conclusion: Bone scintigraphy-derived joint assessment significantly correlated with PET/CT derived joint counts. Bone scintigraphy could serve as a sensitive and reliable method for evaluating disease activity in RA patients.


Disclosure of Interests: None declared DOI: 10.1136/annrheumdis-2020-2020.5727

THU0104 THE GUT MICROBIOTA AND ITS RELEVANCE TO PERIPHERAL T REGULATORY CELLS AND T HELPER 17 IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a common autoimmune disorder with joint destruction and synovial inflammation characterized by abnormal immune responses to autoantigens. Our previous studies have demonstrated that impaired peripheral lymphocytes especially insufficiency of regulatory T cells (Tregs) played an important role in pathogenesis of RA. Interestingly, the dysbiosis of gut microbiota triggers several types of autoimmune diseases through the imbalance of T lymphocyte subsets. However, the detailed gut microbiota of RA patients and its correlation with Tregs and helper T cells 17 (Th17) are unclear up until now.

Objectives: To compare the difference of gut microbiota between RA and healthy controls (HCs), and to investigate the relevance of gut microbiota with circulating Tregs and Th17 in patients with RA.

Methods: From December 2018 to August 2019, a total of 205 diagnosed patients with RA and 199 age and sex-matched HCs were enrolled in this study. Stool of each participant was collected for bacterial DNA extraction and 16S ribosomal RNA (rRNA) gene sequencing. The absolute numbers of Tregs and Th17 in PB of these individuals were measured by Flow Cytometry (FCM) combined with standard absolute counting beads. Data were expressed as mean ± standard deviation to the distribution. Independent-samples T test and Spearman rank correlation test. P value <0.05 were considered statistically significant.

Results: Patients with RA had a significantly difference of diversity and abundance of intestinal microbiota compared with those of HCs (P < 0.05). Detailedly, the abundance of Proteobacteria was significantly increased in RA patients (P < 0.05), and the abundance of Firmicutes, Fusobacteria and Verrucomicrobia was significantly reduced (P <0.05) at the level of Phylum (Figure 1). At the genus level, in the RA group, the abundance of Escherichia, Ruminococcus2 and Clostridium_sensu_stricto were significantly increased (P < 0.05), but the abundance of Lachnospiraceae_incertae_sedis, Prevotella, Clostridium_XIVa, Roseburia, Dialister, Blautia, Megamonas and Gemmiger were significantly lower than the healthy controls (P < 0.05) (Figure 2). Moreover, Blautia, Anaerostipes and Ruminococcus2 have negative correlation with the absolute number of Tregs, and Cloacibacillus and Streptophyta have positive correlation with the absolute number of Th17.

Conclusion: Patients with RA had a dysbiosis of the gut microbiota in both diversity and abundance, which is closely related to the impaired peripheral lymphocyte subsets, that may be related to the pathogenesis of RA, which might provide a new idea for RA treatment.


THU0105 ISOTOPE-LABELING-LC-MS-BASED METABOLIC PROFILING OF MULTIPLE SERUM SAMPLE SETS FOR THE DISCOVERY OF HIGH-CONFIDENCE RHEUMATOID ARTHRITIS BIOMARKERS

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Background: Early diagnosis of rheumatoid arthritis (RA) is hampered by suboptimal accuracy of currently available serological biomarkers. Metabolomics may reveal promising biomarker candidates associated with the biomolecular processes of RA. In this work, we applied a high-performance chemical isotope labeling (CIL) LC-MS technique for in-depth profiling of the amine/phenol-submetabolome in serum samples. To avoid false positives and obtain high-confidence biomarker candidates, we analyzed three independent sets of serum samples collected from RA patients and healthy controls to examine the common metabolic fingerprints.

Objectives: We aimed to identify a metabolite signature with consistently high accuracy for RA.

Methods: Serum samples were taken from 3 RA cohorts, which comprised 50, 49, and 131 RA patients, respectively. Within each cohort, there were

Acknowledgments: None

Disclosure of Interests: None declared DOI: 10.1136/annrheumdis-2020-2020.2718

THU0106 GUT MICROBIOTA DURING TREATMENT WITH THE BIOLOGICS INFliximab OR ETANERCEPT IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Researchers have recently described significant alterations in the gut microbiota of patients with rheumatoid arthritis (RA) compared to healthy controls (HCs). These changes may be associated to the regulation of immune responses and the pathogenesis of RA. To explore the impact of biological therapy on the gut microbiota, we evaluated the microbial composition and diversity of patients with RA before and during treatment with infliximab (IFX) or etanercept (ETA).

Objectives: We aimed to compare the gut microbiota of patients with RA before and during treatment with IFX or ETA to identify potential biomarkers of treatment response.

Methods: We recruited 20 patients with RA who had never received biologic therapy and were treated with IFX or ETA. Patients were monitored for 1 year. Gut microbiota was analyzed using a high-throughput sequencing method before and during treatment.

Results: Before treatment, the gut microbiota of patients with RA showed significant differences compared to HCs, with a reduction in the abundance of beneficial gut bacteria such as Faecalibacterium prausnitzii and an increase in potentially harmful bacteria such as Enterobacteriaceae. During treatment, the gut microbiota of patients with RA showed a trend towards recovery, with an increase in the abundance of F. prausnitzii and a decrease in Enterobacteriaceae. The treatment response was associated with a decrease in inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate.

Conclusion: Treatment with IFX or ETA may have a positive impact on the gut microbiota of patients with RA, improving the balance of beneficial and potentially harmful gut bacteria. Further studies are needed to confirm these findings and to identify specific gut microbiota signatures associated with treatment response.